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(54) Title: EMULSIONS AND AQUEOUS DISPERSIONS OF PHYTOSTEROLS

(57) Abstract: Phytosterols can be dispersed at high concentrations in aqueous media by partial neutralization of the inherent phytosterol w/o emulsifying properties using a non-sterol emulsifier having a higher HLB value. A preferred non-sterol emulsifier is a lecithin preparation comprising lysolecithin. These low-viscosity aqueous phytosterol dispersions can be used to prepare blood cholesterol lowering, stable w/o emulsions such as spreads and margarine.

Emulsions and aqueous dispersions of phytosterols

Field of the Invention

The present invention relates to edible compositions having an aqueous phase and comprising phytosterol(s) in the aqueous phase, to a method for preparing such compositions, and to the use of these compositions in preventing or treating hypercholesterolemia and other medical conditions.

Background of the Invention

The cholesterol-lowering effects of dietary plant sterols have been recognized for over 50 years. In the intestinal lumen cholesterol is found in solution with other fats in micelles composed of bile salts, phospholipids, tri-, di- and monoglycerides, fatty acids and fat-soluble micronutrients. In the process of absorption, cholesterol in the micelles is transported across the intestinal lining and into the lymph. It is generally accepted that there are two possible mechanisms by which plant sterols can inhibit absorption of cholesterol from the small intestine: co-precipitation of cholesterol and plant sterols, and competition for space in mixed micelles.

According to the co-precipitation mechanism, when the poorly-absorbed plant sterols reach a critical concentration in the gut they precipitate out of solution, bringing cholesterol down with them. The precipitated crystalline cholesterol is insoluble and cannot be absorbed.

The alternative mechanism is related to the limited capacity in the mixed micelles for carrying cholesterol. Competition for this space by structurally similar plant sterols has the effect of restricting the amount of cholesterol that can be transported into the intestinal cells via the micelles.

The highly hydrophobic nature of phytosterols renders them insoluble and barely dispersible in aqueous media. For convenience, phytosterols tend to be added to the fat phase of fat-based food products. Health-conscious consumers wishing to benefit from the cholesterol-

lowering effects of phytosterols are therefore forced to consume fat-rich foods, despite the health risks of a high fat diet.

Since phytosterols have high melting points (typically about 136-150°C) it is important to maintain a temperature of 80°C or higher during dissolution of phytosterols in fats or oils, in order to avoid recrystallisation of the phytosterols. Crystalline phytosterol imparts an unpleasant grainy, waxy texture to edible and topical products. However, at 80°C and above commonly used fats and oils are vulnerable to oxidation. Rancid oils and fats detract greatly from the organoleptic properties of food products in particular.

The problems associated with adding phytosterols to the fat phase are compounded in low fat, fat-based products. The amount of phytosterol capable of being dispersed in the fat phase of a fat-based emulsified product directly correlates with the amount of lipid in the product. Thus, when the lipid content is reduced to below a certain level it becomes technically impossible to incorporate enough phytosterol into an edible product to obtain a tangible health benefit. The problems posed by the need to disperse phytosterols in fat become more acute the lower the fat content of a fat-based product. Although the fat-solubility of phytosterols can be improved by esterification, this is not a satisfactory solution to the problem, since phytosterol esters are biologically less efficacious than non-esterified phytosterols. Furthermore, when phytosterol or phytosterol ester is distributed within the small volume lipid phase of a low fat emulsified product the taste of the product is adversely affected, since the high concentration of phytosterol in the fat leads to a waxy sensation in the mouth and on the tongue.

In view of the technical difficulties involved in adding phytosterols to fat in foods, and bearing in mind public demand for low-fat and fat-free products, it would be advantageous to find an effective means of dispersing or suspending phytosterols in aqueous media at high concentrations, thereby opening up the possibility of providing low fat or fat-free products containing phytosterols in a variety of formats.

Although the solubility of phytosterols in water has been shown to be improved to some extent through use of food-grade water-in-oil (w/o) emulsifiers such as lecithin, optionally in the presence of a coating material, the resulting dispersions are frequently very viscous,

non-homogenous, have poor mouth-feel, and are unstable (liable to separate) and difficult to handle. There is a particular tendency for phytosterol in these dispersions to solidify. This can cause severe processing difficulties in the manufacture of phytosterol-containing products on an industrial scale. For example, heat and mechanical energy are applied in the preparation of w/o or o/w emulsions. Under these conditions of elevated temperature and vigorous mixing the presence of phytosterol in an emulsion promotes premature solidification, thereby causing blockages in the processing machinery.

The present invention concerns a new technique allowing unprecedentedly large amounts of phytosterol to be dispersed in an aqueous medium without causing adverse effects on mouth-feel. The resulting dispersions and emulsions made using these dispersions are stable, have low viscosity, and are easy to handle during downstream processing steps. This novel dispersion technique has broad applications not only within the food industry, but also to pharmaceutical manufacturing and to cosmetics.

Summary of the Invention

In a first aspect of the invention there is provided a method of preparing a product comprising phytosterol dispersed in an aqueous phase, which comprises mixing particulate phytosterol with an aqueous medium in the presence of a non-sterol emulsifier having a HLB value higher than that of the phytosterol to create an aqueous phytosterol dispersion, such that the combined HLB value of the non-sterol emulsifier and the phytosterol in the aqueous phase does not exceed 8.

According to a second aspect of the invention there is provided a method of preparing an emulsified product comprising phytosterol dispersed in an aqueous phase, which comprises mixing particulate phytosterol with an aqueous phase, adding a non-sterol emulsifier having a HLB value of at least 7 to the aqueous phase and/or to a fat phase, and mixing together the aqueous phase and the fat phase to form an emulsion.

According to a third aspect of the invention there is provided a composition obtainable by the preparative method of the invention.

According to a fourth aspect of the invention there is provided a composition having an aqueous phase comprising a stable dispersion of a phytosterol and a phospholipid emulsifier having a HLB value ≥ 7, wherein the weight ratio of phytosterol:phospholipid emulsifier in the aqueous phase is greater than 1:1, and the combined HLB value of the phospholipid emulsifier and the phytosterol in the aqueous phase does not exceed 8.

According to another aspect of the invention there is provided an emulsion having an aqueous phase comprising a phytosterol and a lipid phase comprising a phospholipid emulsifier of HLB ≥ 7.

In another aspect of the invention there is provided use of a neutralizing emulsifier to reduce the viscosity of an aqueous dispersion of phytosterol or of an emulsion comprising said aqueous dispersion, particularly where said dispersion comprises a thickening agent.

In a further aspect of the invention there is provided use of a neutralizing emulsifier to stabilize an emulsion comprising a fat phase and an aqueous phase comprising phytosterol, wherein the neutralizing emulsifier is in the aqueous phase or in the fat phase or distributed between the aqueous phase and the fat phase.

In yet another aspect of the invention there is provided use of a composition of the invention as a medicament.

In a further aspect of the invention there is provided use of a composition of the invention in the manufacture of a medicament or therapeutic nutritional formulation for the prevention or treatment of any of: elevated blood cholesterol levels, hypertriglyceridemia, coronary heart disease, diabetes, atherosclerosis, inflammation, osteoarthritis, breast cancer, colon cancer, and benign prostatic hyperplasia.

Description of the Figures

Figure 1 is a flowchart depicting a preferred method of manufacture of a spread according to the invention.

Detailed Description of the Invention

It has not previously been reported that the inherent water-in-oil emulsifying properties of phytosterols contribute to the difficulties encountered in creating and using aqueous dispersions of phytosterols, and emulsions comprising such dispersions. We have now achieved surprising and dramatic technical improvements in the properties of compositions containing water-dispersed phytosterols by applying the preparative method of the invention, particularly in the context of emulsions containing a fat phase.

Through use of one or more neutralizing emulsifiers (e.g. any oil-in-water emulsifier) in the aqueous phase or in the fat phase in conjunction with phytosterol in the aqueous phase, preferably such that the combined HLB of emulsifying phytosterol plus added non-sterol emulsifier(s) does not exceed 8, a surprisingly stable aqueous dispersion or emulsion of unexpectedly low viscosity is obtained.

It seems that the neutralizing emulsifier, whether in the aqueous phase, or the lipid phase of an emulsion, or distributed over both phases, manages to counteract some of the inherent w/o emulsifying activity of the phytosterol, preventing clumping together of phytosterol microparticles, formation of which is a major factor contributing to the viscosity and solidifying tendencies of phytosterols in aqueous media and in emulsions. The viscosity-reducing effect of the non-sterol emulsifier is particularly marked when a stabilizing thickener such as alginate is added to an aqueous dispersion containing phytosterol. Use of the neutralizing emulsifier enables high levels of thickener to be used without unduly increasing the viscosity. Thus, the rheological properties of the dispersion are dramatically improved by use of a neutralizing emulsifier.

Furthermore, use of the neutralizing emulsifier counteracts the inherent instability of emulsions obtained by mixing a fat phase and a water phase containing high levels of phytosterol. The aqueous phytosterol dispersions of the invention can be used in the large-scale manufacture of emulsions containing high levels of phytosterol over a broad range of temperatures and under vigorous mixing conditions, without the drawback of breakdown of the emulsions and high viscosity.

The mouth feel (bitterness, texture, grainy feel) of phytosterol in an aqueous dispersion or in the aqueous phase of an emulsion is improved through use of the neutralizing emulsifier, particularly when that emulsifier is phospholipid-based.

The method of the present invention makes it possible to include phytosterols at effective levels in the aqueous phase of a broad range of nutritional, cosmetic and pharmaceutical products, thereby opening up new formulation opportunities, such as low fat and fat free formulations.

In the present context the generic term "sterol" or "phytosterol" is intended to encompass any member of the family of free phytosterols (non-hydrogenated) and phytostanols, and esters or other derivatives thereof, and any mixture or combination thereof.

The phytosterols used in the invention may be chemically synthesized, or may be derived from natural sources, including plant sources such as avocado, soy, rice bran, tall oil pitch or soap, shea nut, coconut, and plant oils, for example rapeseed, soya, maize, sunflower and sesame oils. Some germ oils are very rich in phytosterols, wheat germ and oats being good examples. Non-exhaustive examples of plant sterols include sitosterol, stigmasterol, campesterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, avenasterol, and clionasterol, and their correspondlng stanols.

The phytosterols are provided in particulate powder form for use in preparing the dispersions of the invention. Dispersion is facilitated by using finely divided phytosterols, preferably where 95% of the particles have a size (diameter) of less than 100μm, preferably less than 30μm and most preferably less than 15μm. Usually, the particle size distribution will be such that 90% of the particles are in the range 100nm to 35μm, more preferably 0.2 to 20μm, and most preferably 0.5 to 15μm. Particle mixtures with this size range can be prepared by standard milling techniques, such as by use of an air mill, high energy hammermill, disc mill, or air filtration mill. Optionally, the phytosterol is milled in the presence of sugar, and the powdered phytosterol/sugar mix is used in the preparation of sweetened food or nutritional products.

In the finished product (an aqueous dispersion, or an emulsion comprising the aqueous dispersion) the amount of phytosterol is preferred to be between about 0.5% and 20% by weight of the product, more preferably 1% to 15%, and most preferably 2% to 10% by weight, for example 3 to 8% by weight. In an emulsified product, the phytosterol in the aqueous phase may constitute 1-80 wt%, more preferably from 5-50 wt%, especially 7-25%, by weight of the aqueous phase.

The terms "neutralizing emulsifier", "neutralizing non-sterol emulsifier" and "o/w emulsifier" are used interchangeably herein.

The neutralizing non-sterol emulsifier has a HLB (Hydrophilicity-Lipophilicity Balance) value which is higher than the HLB of the phytosterol in the aqueous phase, usually in the range 6-20, preferably 7 to 12. The HLB system is a scale used for describing the characteristics of a surface-active agent. Detailed information on the HLB system and determination of HLB values can be found in the Kirk-Othmer Encyclopedia of Chemical Technology, (3rd Ed.) 8: pp 910-918, which is incorporated herein by reference. Emulsifiers having HLB values in the range 7 to 18, especially 8 to 18, are often termed oil in water (o/w) emulsifiers. W/o emulsifiers have HLB values in the range 1-9, especially 1-6. Since HLB numbers are additive, the overall HLB value of a blend of emulsifiers of known HLB can easily be calculated.

In general, a single non-sterol emulsifier is used to neutralize the phytosterol.

Suitable neutralizing emulsifiers for use in the invention include phosphatides of HLB at least 7 (e.g. lysophosphatides), especially phosphoglycerides such as phospholipids and lysophospholipids. Lecithin preparations (E322) of suitably high HLB are particularly preferred, and among this group lecithin preparations containing at least 90 wt%, preferably at least 95 wt%, of acetone insoluble compounds (mostly phospholipids) are preferred. Preparations of this sort have a low triglyceride content and are obtainable by dissolving away triglycerides from an impure lecithin preparation using acetone. Emultop™ (Lucas Meyer) and SternPure E™ (Stern) are suitable lecithin emulsifiers. Preferably, the lecithin preparations used in the invention will comprise at least 3 wt%, and more preferably at least 5 wt%, of lysolecithin. Lecithin preparations comprising lysolecithin can be prepared from lecithin (e.g. soya lecithin or yolk lecithin) by enzymatic hydrolysis using snake venom

phospholipase A2. A preferred lecithin preparation is one having a HLB value of between 8 and 10, preferably 8-8.5.

Other neutralizing emulsifiers are [HLB values in brackets]: gelatin [9.8], sorbitan monolaurate [8.6], sodium oleate [18.0], potassium oleate [20.0], methylcellulose [10.5], acacia [12.0], tragacanth [13.2], triethanolamine oleate [12.0], polyoxyethylene monooleate [11.4], polyoxyethylene monostearate [11.6], polyoxyethylene monolaurate [13.1], polysorbates/Tweens [8 to 18] (specific examples being polyoxyethylene sorbitan monostearate (Tween 60/Tween 61) [14.9/9.6], polyoxyethylene sorbitan monooleate (Tween 80/Tween 81) [15/10], polyoxyethylene sorbitan monolaurate (Tween 20/Tween 21) [16.7/13.3], polyoxyethylene sorbitan monopalmitate (Tween 40) [15.6], polyoxyethylene sorbitan trioleate [11.0]), glyceryl esters [8-13], ethoxylated monoglycerides [12-14], sugar esters [>7; e.g. 11-15], citric acid esters of mono and diglycerides, Lactem™, Citrem™, Datem™,and so on.

According to one embodiment of the invention when the phytosterol and neutralizing emulsifier are dispersed together in an aqueous medium, the HLB of the combination of all emulsifying components (including phytosterol and neutralizing emulsifier) in the aqueous dispersion exceeds that of the phytosterol component(s), and is ≤8, preferably lying in the range of about 1 to 8, more preferably between 3 and 6.

The amount of the non-sterol emulsifier in the aqueous dispersion, as a proportion of the finished product (e.g. an emulsion), is generally between 0.01 and 1% by weight, and most preferably about 0.5%, such as between 0.25 and 0.45%. Phytosterol is preferably in weight excess relative to the non-sterol emulsifier(s) in the aqueous dispersion. The relative weight proportions of phytosterol and non-sterol neutralizing emulsifiers present in the aqueous dispersion of the invention are optionally between 4:1 and 500:1, preferably between 7:1 and 50:1, and generally between 10:1 and 30:1.

According to another embodiment of the invention the phytosterol is dispersed in an aqueous medium, and the neutralizing emulsifier is incorporated into a lipid medium, and an emulsion is prepared by mixing both media together. In this embodiment, too, the neutralizing emulsifier counteracts the low HLB of the phytosterol and stabilizes the emulsion formed when the aqueous phase and fat phases are mixed together. The

phytosterol is preferably in weight excess relative to the non-sterol neutralizing emulsifier in the emulsified product, for instance in a dry weight ratio of 4:1 to 500:1, preferably 7:1 to 50:1, and generally 10:1 to 30:1. Optionally, the neutralizing emulsifier is distributed over both phases of the emulsion, preferably in the range 1:9 to 9:1 parts by weight (fat phase content:aqueous phase content).

In a preferred embodiment of the invention the aqueous phytosterol-containing dispersion is mixed directly with a lipid composition to create a very stable emulsion having a fat phase and a water phase, the phytosterols being primarily localized to the water phase. The emulsified fat based products created in accordance with the invention may be oil-in-water (o/w, or water continuous) or water-in-oil (w/o, or oil continuous) emulsions according to which emulsifiers are selected for use in preparing the emulsion. W/o emulsions are preferred. For the manufacture of enteral pharmaceutical and nutritional products, such as edible spreads, margarines, and icings/frostings it is usual to generate a w/o emulsion. Salad dressings and infant formulas are generally o/w type emulsions. Preparations for external application may be either o/w or w/o emulsions. Optionally, multiple emulsions of the w/o/w or o/w/o type can also be prepared.

In an emulsion made in accordance with the invention the weight proportion of the aqueous phase:fat phase can vary according to the intended application of the emulsion. For edible compositions this ratio usually varies between 1:8 and 8:1. Regular yellow fat spreads and margarines contain up to 85% by weight of fat. Low fat spreads may contain 45-65% fat. Very low fat spreads comprise 30% fat or lower. For regular salad dressings the level of fat is generally from 10-60%, more preferably from 15-40% by weight of the product. Low fat salad dressings can contain as little as 0-10% by weight of lipids.

In the emulsified products of the invention the fat phase preferably comprises one or more vegetable oils, such as sunflower oil, soybean oil, rapeseed oil, canola oil, corn oil, peanut/groundnut oil and the like. Dairy and other animal fat may also be used. Other lipid substances in the fat phase can include petroleum-derived waxes and oils. If desired the fat may be hydrogenated, fractionated and/or interesterified. For edible compositions it is preferred for the fat in the fat phase to comprise polyunsaturated fatty acids, PUFAs preferably contributing at least 30%, or more preferably at least 45%, of the fat phase by

weight. Natural oils rich in PUFAs are the preferred source, some examples being sunflower, rapeseed, linseed, linola and/or soybean oils.

An advantage of the present invention is that it circumvents the need to add a w/o emulsifier to the fat phase of an oil continuous product, which is standard practice in commercial manufacturing of such products. The partially-neutralized inherent w/o emulsifying activity of the phytosterol aqueous phase suffices to create a stable w/o emulsion. Therefore, in one embodiment of the invention w/o emulsifiers are omitted from the lipid phase in the formation of an oil continuous fat-based product.

In certain circumstances emulsifiers may be employed in the fat phase, optionally in addition to the neutralizing phospholipid emulsifier, for example where an o/w emulsion is prepared. Additional emulsifiers can include: anionic surfactants such as alcohol ether sulfates, alkyl sulfates, soaps and sulfosuccinates, sodium dodecyl sulfate (SDS), mono and diacylglycerides and derivatives thereof, e.g. Acetem™, Lactem™, Citrem™, Datem™; cationic surfactants such as quaternary ammonium compounds; zwitterionic surfactants such as alkyl betaine derivatives; amphoteric surfactants such as fatty amine sulfates, difatty alkyl triethanolamine derivatives, phospholipids, lecithins, lysolecithins; and non-ionic surfactants such as the polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, saturated fatty acids and alkylphenols, water-soluble polyethyleneoxy adducts onto polypropylene glycol and alkyl polypropylene glycol, nonylphenol polyethoxyethanols, castor oil polyglycol ethers, polypropylene/polyethylene oxide adducts, tributylphenoxy-polyethoxyethanol, polyethylene glycol, octylphenoxy-polyethoxyethanol, lanolin alcohols, polyethoxylated (POE) alkyl phenols, POE fatty amides, POE fatty alcohol ethers, POE fatty amines, POE fatty esters, poloxamers (7-19), POE glycol monoethers (13-16), polysorbates and sorbitan esters, and glyceroglycolipids. In a preferred embodiment the fat phase of an emulsion made according to the invention comprises mono- and diglycerides.

Optionally, the emulsifier added to the fat phase is phytosterol. Thus, in accordance with the present invention it is possible to provide a finished edible composition containing large amounts of phytosterol distributed over both phases.

The amount of emulsifier required to be added to the fat phase varies according to the identity of the emulsifier, the type of emulsion, the material to be emulsified and the

presence of stabilizing ingredients, but generally lies in the range 1-20% by weight of the lipid. For instance, the emulsion may comprise 0.05 to 1%, preferably 0.05 to 0.5% by weight of mono and diglycerides. Exact amounts for particular applications can easily be determined by the skilled person. These will usually not need to be as high as levels used in conventional margarine manufacture, for instance, since their presence is only required where the emulsifying power of the partially neutralized phytosterols is insufficient to stabilize the emulsion.

As emulsion stabilizers, gelling agents, fat replacers and thickeners it is possible to use any conventional products suited for these purposes, especially those permitted for use in food products. Examples include, but are not limited to, lyophilic colloids such as polysaccharides including acacia gum, agar, alginic acid, carrageenan, guar gum, gellan gum, carob gum, konjac gum, karaya gum, tragacanth, locust bean gum, xanthan gum, cellulose gums, gel-forming starches (e.g. from corn, amaranth, oats, tapioca, rice and potato), modified food starches, polydextrose, maltodextrin, cyclodextrins, pectin, cellulose and its methylated derivatives, microcrystalline cellulose (MCC), inulin, oatrim, curdlan; amphoterics (e.g. gelatin); fibers; proteins or peptides (e.g. Microparticulated Protein Product MPP or whey protein-based thickeners); and synthetic or semi-synthetic polymers (e.g. carbomer resins, cellulose ethers, carboxymethyl cellulose (CMC), carboxymethyl chitin, polyethylene glycol-n (ethylene oxide polymer $H(OCH_2CH_2)_nOH$); finely divided solids including clays (e.g. attapulgite, bentonite, hectorite, kaolin, magnesium aluminium silicate and montmorillonite), microcrystalline cellulose oxides and hydroxides (e.g. aluminium hydroxide, magnesium hydroxide and silica); and cybotactic promoters/gellants including amino acids, lecithin and other phospholipids and poloxamers.

Maltodextrin and/or alginate are the preferred stabilizers for addition to the aqueous phytosterol dispersion.

The amount of emulsion stabilizer/thickener to be included in the compositions of the invention depends on the consistency desired in the end product. Usual amounts lie in the range 0 to 30%, preferably 0.1 to 25% based on the weight of the aqueous phase of the product.

In a preferred procedure for preparing an aqueous dispersion in accordance with the invention, the phytosterol is provided in particulate, powder form and pre-mixed with other powdered ingredients (excluding the non-sterol emulsifier and any thickener), before addition of the pre-mix to hot water (60°C to 85°C) or other aqueous medium. The powdered non sterol (o/w) emulsifier is then added to the aqueous medium containing the phytosterol. Alternatively, the powdered phytosterol and powdered non-sterol (o/w) emulsifier are added together (e.g. as a pre-mix, or simultaneously) to the heated aqueous medium. Once all the emulsifying ingredients are well dispersed it is possible to add thickening agents to the mix.

Addition of the phytosterols to the aqueous medium should be slow. Other optional components of the aqueous medium include gelling agents, fat replacers, and the like. The phytosterol-emulsifier complex in the aqueous medium is prepared by vigorous mixing, such as high shear mixing, e.g. by stirring, by turbine agitation, by propeller agitation, by microfluidization, by use of a centrifugal pump in standard Ventouri equipment, by use of a colloid mill or ball mill, by homogenization, by vortexing, by sonicating or by passing through a small orifice (e.g. in a French press).

Preferably, the aqueous medium comprising phytosterol and non-sterol (o/w) emulsifier is maintained at a temperature of between 60 and 100°C, generally about 80°C, and stirred until the phytosterol is evenly dispersed. At this point a milky suspension is obtained. The dispersion is kept under continuous agitation and, optionally, further water-soluble or water-dispersible ingredients are added to the suspension at this point: for example milk powder or protein, vegetable protein, colorings, flavorings, acidulants, preservatives, vitamins, salts, and so on. The aqueous phytosterol dispersion/suspension is phase-stable. This generally means, for example, that no phase separation is visible after at least 5 minutes, preferably after at least 30 minutes, and more preferably after at least 2 hours.

The aqueous dispersion may be used as such in preparing any liquid food, beverage, topical formulation or medicament. Alternatively the aqueous dispersion may be dried, for example by lyophilization or spray-drying, and then used in powdered form in a variety of applications.

In another embodiment of the invention the aqueous dispersion is employed (usually without an intermediate drying step) in the manufacture of an emulsified product comprising

a fat phase and a water phase. W/o or o/w emulsions of this type can be prepared by any technique known in the art.

When the non-sterol neutralizing emulsifier is to be added to the fat phase of an emulsion it is melted into the fat blend that contains all the other fat ingredients, which is subsequently mixed with a phytosterol-containing aqueous phase (optionally prepared as described above).

According to a preferred process an aqueous dispersion of phytosterol (with or without the neutralizing non sterol emulsifier) is mixed with pre-heated lipid (oil or fat). Preheating is carried out at 50-60°C (preferably about 55°C). The pre-heated lipid comprises the non-sterol neutralizing emulsifier of the invention if none is already present in the aqueous dispersion or in addition to that added to the aqueous dispersion, and sometimes other emulsifiers which are lipid-soluble, such as lecithin, monoglycerides and diglycerides. An emulsion is created by mixing together the aqueous blend with the fat blend. Further processing of the emulsion depends on the intended use of the emulsion. In the preparation of margarines, spreads and the like, the emulsifying step is followed by pasteurization, crystallisation and filling, which are standard procedures in the art.

The lipid used to make the emulsions may comprise additional fat-soluble components which are customary additives in the art, for example stabilizers, coloring agents, flavoring agents, pH regulators, vitamins (e.g. vitamins A & D), salts, anti-bacterial agents, antioxidants and preservatives. In the case of spreads and margarines the preferred antioxidants are tocopherols.

Emulsified w/o products made by the preparative method of the invention are particularly phase stable and can be stored and transported under demanding conditions without exhibiting a tendency to separate.

The nutritional product formats which are envisaged to incorporate the aqueous dispersion of the invention include: emulsified fat spreads or margarine, shortenings, cheese, mayonnaise, ice-cream, salad dressing, yoghurt, smoothies, chocolate, puddings, dairy desserts, coffee whitener, custards, dairy beverages, milk-shakes, icings, baked products, cake mixes, noodles, pasta, granola bars, soups, infant formulas, and the like.

Medical nutrition products comprising the dispersion of the invention include enteral and parenteral complete formula diets, in liquid form or lyophilized for later reconstitution, and medical feeding supplements. Products formulated for enteral feeding may be intended for tube feeding or for oral administration, either in hospitals or in the home. The medical nutrition products may be formulated having regard to the needs of particular patient types, such as diabetics, heart disease patients, stroke patients, arthritis sufferers, cancer patients, and anyone at risk of developing these diseases.

The nutritional products according to the invention may be non-fat products, low fat products or very low fat products. By "low fat" is generally meant a product, such as a yellow fat spread, comprising less than 45% (e.g. 35-40%), preferably less than 35%, by weight fat. A "very low fat" product has less than 30% by weight fat.

This invention makes possible the provision of phytosterols in oral pharmaceutical dosage forms, particularly solid forms, including tablets, capsules, dragées, granules, pellets, chews, solutions, syrups, lozenges, and powders. Parenteral emulsions can also be prepared for administration to severely-debilitated patients. Customary pharmaceutical excipients, diluents and stabilizers may be employed.

Topical cosmetic and pharmaceutical formulations incorporating the emulsions of the invention include salves, creams, foams, lotions, gels, soaps, shampoos, and the like.

The pharmaceutical, food or drink products may be supplemented with other health-promoting ingredients, particularly ingredients known to have benefits for the cardiovascular system. Non-limiting examples are PUFAs, polyphenols, lipid-soluble antioxidants (e.g. tocopherol, tocotrienols, lycopene), water-soluble antioxidants (e.g. ascorbate), amino acids, dietary fibers, vitamins, minerals and the like.

Pharmaceutical, food or beverage products incorporating water-dispersed phytosterols can be consumed safely by anyone, but conveniently form part of the diet of those with a propensity to having high blood cholesterol levels. According to one aspect of the invention a method is provided for preventing or treating high blood cholesterol levels comprising administering, to a person in need of such treatment, a composition having an aqueous

phase comprising a stable dispersion of a phytosterol and a phospholipid emulsifier having a HLB value ≥ 7, wherein the weight ratio of phytosterol:phospholipid emulsifier in the aqueous phase is >1, and the combined HLB value of the phospholipid emulsifier and the phytosterol in the aqueous phase does not exceed 8. By "high blood cholesterol" is meant: over 200mg/dl, especially over 240mg cholesterol/dl blood; and/or a ratio total cholesterol/HDL of 5:1 or greater; and/or an LDL blood concentration of greater than 130mg/dl, especially over 160mg/dl. The pharmaceutical and nutritional products of the invention play a role in reducing blood cholesterol levels and thereby preventing cardiovascular disease and heart disease.

Aside from hypercholesterolemia, other indications for which phytosterols may deliver a health benefit include: hypertriglyceridemia, coronary heart disease, diabetes, atherosclerosis, inflammation, osteoarthritis, breast cancer, colon cancer, and benign prostatic hyperplasia. Therefore the invention also provides a method of preventing or treating elevated blood cholesterol levels, hypertriglyceridemia, coronary heart disease, diabetes, atherosclerosis, Alzheimer's disease, inflammation, osteoarthritis, breast cancer, colon cancer, or benign prostatic hyperplasia comprising administering, to a person in need of such treatment, any composition of the invention as defined hereinbefore.

Examples

Example 1: Properties of aqueous phytosterol dispersions made with different emulsifiers

Aqueous dispersions were prepared having the compositions set out in Table I.

Table 1

Component	wt %
Water	82
Phytosterols blend	10
Bodying agent	4.6
Thickener (or water)	1.2
Milk protein	0.9
Acidifying agent	0.09
Salt	0.3
Preservative	0.12
Emulsifier (or water)	0.69

The emulsifiers tested were Emultop (Lucas Meyer), Bolec C lecithin emulsifier of HLB approx. 3 and Tween 60 (polysorbate) emulsifier of HLB approx. 15.

In each case all of the powder ingredients (including the emulsifiers Emultop and Tween 60, but excluding Bolec C) were mixed together before blending with water at 85° C using a high shear mixer. As Bolec C has a low affinity for water it was added last to the aqueous mix of other ingredients.

For testing the mouthfeel (bitterness, texture, sandiness) the dispersions were maintained at room temperature. Observations on stability were made after holding the mixtures for 2 hours in a graduated cylinder held in a water bath at 40°C. Viscosity was determined using a Brookfield viscometer, spindle #3, speed 60 rpm, at 40°C. Table 2 presents the results of these tests.

Table 2

Emulsifier		Bolec C (with thickener)	Tween 60 (with thickener)	Emultop (with thickener)	None (with thickener)	None (without thickener)
Mouthfeel	Bitterness	slight	strong (from phytosterol and Tween)	slight	strong (from phytosterol)	very slight
	Texture	very thick	thin	thick	thick	thin
	Sandiness	slight	none	none	none	none
Stability		Good	Good	Good	Good	Phase separation (15% of clear liquid at the bottom)
Viscosity		900 mPa.s	120 mPa.s	350 mPa.s	550 mPa.s	N.D.

Table 2 shows that when attempts are made to dissolve phytosterols in water with the addition of a thickener the resulting dispersion is highly viscous and has an unpleasant taste. The absence of a thickener results in phase separation.

Bolec C is a lecithin w/o emulsifier of low HLB. It can be seen from Table 2 that use of such an emusifier results in an aqueous dispersion of very high viscosity and thick texture, which also has a slightly sandy feel.

Tween 60, a high HLB emulsifier improves the viscosity of a phytosterol-containing water dispersion, but it fails to mask the unpleasant bitter taste of the phytosterols, and moreover contributes an unpleasant taste of its own.

Emultop, which is a non-sterol lecithin emulsifier used in accordance with the invention, succeeded in moderating the viscosity of the aqueous phytosterol dispersion and simultaneously reducing the bitter taste of the phytosterol. These properties are optimal for

preparing edible formulations containing phytosterol which are easily manageable during processing, have a long shelf life, and appeal to the consumer for taste reasons as well as for health benefits.

Example 2 : Viscous properties of emulsions made according to the invention

An emulsion was prepared consisting of 35% fat phase (containing a mix of vegetable oils) and 65% water phase containing phytosterols (Reducol™; Novartis Consumer Health), alginate thickener and Emultop™ lecithin emulsifier (Lucas Meyer) of HLB ±8, such that the concentrations of components in the emulsion were:

blend of phytosterols	6.6 wt%
alginate thickener	0.8 wt%
Emultop emulsifier	0.15/0.30/0.60 wt%

(+ minor amounts of salt, preservatives and acidifier)

It was not possible to prepare a control emulsion lacking emulsifier altogether, because the emulsions was not stable.

The viscosity of the emulsion was measured using a Brookfield viscometer DV-1,spindle size c, at 50°C following the usual method known for viscosity measurement of shear thinning fluids after 30 minutes mixing time (mixing velocity 800 rpm), at a temperature of 50°C. The results are illustrated in Table 3.

Table 3

Emultop Level (in emulsion)	Viscosity (cP.s)
0.15%	5260
0.30%	4630
0.60%	3990

It is clear from this experiment that within the range 0.15-0.60%, the higher the concentration of emulsifier such as Emultop (of high HLB) the greater the reduction in viscosity of an emulsion containing phytosterols, thereby facilitating processing of the emulsion, for instance in the preparation of fat spreads.

In an analogous experiment, when Emultop was added to the fat phase instead of the water phase it was found to deliver comparable benefits in terms of lowering emulsion viscosity. The foam content of the water phase and the emulsion were reduced by putting the Emultop in the fat phase, leading to improved product stability in the plant. However, there was some tendency for separation of the water to occur over time. By sharing the Emultop between the fat phase and the water phase a compromise was achieved, resulting in a stable emulsion product with low foam content.

Example 3: Process for making a low-fat spread comprising phytosterol and Emultop in the aqueous phase

A low-fat spread was prepared by the procedure outlined in the flow chart in Figure 1. The water phase is prepared by heating water up to 85°C and then all the powder ingredients are mixed in using a normal propeller. The oil phase is prepared by premixing the components at 65°C. Then both phases are mixed together in a premix tank and cycles of crystallization are carried out. Filling can be carried out manually or by automation.

The mouthfeel of the resulting spread is comparable with that of conventional low fat spreads.

The spread was found to be stable for more than 2 months at 4°C, and up to 9 hours at 25°C (no oil exudation).

The emulsion generated in the premix tank was not excessively viscous and therefore did not clog the equipment in a manufacturing plant. An analogous emulsion made without neutralizing emulsifier was found to obstruct the pipes, leading to difficulties in pump-assisted phase transfer between tanks, and in emptying the tanks for cleaning.

Claims

1. A method of preparing a product comprising phytosterol dispersed in an aqueous phase, which comprises mixing particulate phytosterol with an aqueous phase in the presence of a non-sterol emulsifier having a HLB value higher than that of the phytosterol to create an aqueous phytosterol dispersion, such that the combined HLB value of the non-sterol emulsifier and the phytosterol in the aqueous phase does not exceed 8.

2. A method according to claim 1 wherein said non-sterol emulsifier has a HLB value of at least 7.

3. A method of preparing an emulsified product comprising phytosterol dispersed in an aqueous phase, which comprises mixing particulate phytosterol with an aqueous phase, adding a non-sterol emulsifier having a HLB value of at least 7 to the aqueous phase and/or to a fat phase, and mixing together the aqueous phase and the fat phase to form an emulsion.

4. A method according to any preceding claim wherein said non-sterol emulsifier comprises phospholipid.

5. A method according to claim 4 wherein said phospholipid comprises lysolecithin.

6. A method according to any preceding claim wherein the particulate phytosterol is added to the aqueous phase prior to, or simultaneous with, addition of the non-sterol emulsifier to the aqueous phase.

7. A method according to any preceding claim wherein 95% of the particles in the particulate phytosterol have a size of between 0.5 and 15μm.

8. A method according to any preceding claim wherein a thickener, such as maltodextrin and/or alginate, is added to the aqueous phase.

9. A composition obtainable by the method of any of claims 1 to 8.

10. A composition having an aqueous phase comprising a stable dispersion of a phytosterol and a phospholipid emulsifier having a HLB value ≥ 7, wherein the weight ratio of phytosterol:phospholipid emulsifier in the aqueous phase is 1:1, and the combined HLB value of the phospholipid emulsifier and the phytosterol in the aqueous phase does not exceed 8.

11. A composition according to claim 10 which further comprises a fat phase.

12. An emulsified composition having an aqueous phase comprising a phytosterol and a fat phase comprising a phospholipid emulsifier having a HLB value ≥ 7.

13. An emulsified composition according to claim 12 which further comprises said phospholipid emulsifier in the aqueous phase of the composition.

14. A composition according to any of claims 10 to 13 wherein the phytosterol comprises non-hydrogenated free phytosterols or esters thereof, or mixtures thereof.

15. A composition according to any of claims 10 to 14 wherein the phospholipid emulsifier is a lecithin preparation.

16. A composition according to claim 15 wherein the lecithin preparation comprises at least 3 % by weight lysolecithin.

17. A composition according to any of claims 10 to 16, wherein the phospholipid emulsifier is present in an amount of 0.01 to 25% by weight of the phytosterol.

18. A composition according to any of claims 10 to 17 wherein said aqueous phase further comprises one or more thickening/gelling agents selected from the group consisting of alginate, gelatin and maltodextrin.

19. A composition according to any of claims 11 to 18 which comprises a water-in-oil emulsion.

20. A composition according to any of claims 10 to 19 which is a nutritional product selected from the group consisting of: an emulsified fat spread or margarine, mayonnaise, ice-cream, salad dressing, yoghurt, chocolate, puddings, dairy desserts, coffee whitener, dairy beverages, icings, and medical nutrition products,

21. A composition according to claim 20 which is a low fat or very low fat nutritional product.

22. Use of a neutralizing emulsifier to reduce the viscosity of an aqueous dispersion of phytosterol or of an emulsion comprising said aqueous dispersion, particularly where said dispersion comprises a thickening agent.

23. Use of a neutralizing emulsifier to stabilize an emulsion comprising a fat phase and an aqueous phase comprising phytosterol, wherein the neutralizing emulsifier is in the aqueous phase or in the fat phase or distributed between the aqueous phase and the fat phase.

24. A composition according to any of claims 10 to 21 for use as a medicament.

25. Use of a composition according to any of claims 10 to 21 in the manufacture of a medicament or therapeutic nutritional formulation for the prevention or treatment of any of: elevated blood cholesterol levels, hypertriglyceridemia, coronary heart disease, diabetes, atherosclerosis, Alzheimer's disease, inflammation, osteoarthritis, breast cancer, colon cancer, and benign prostatic hyperplasia.

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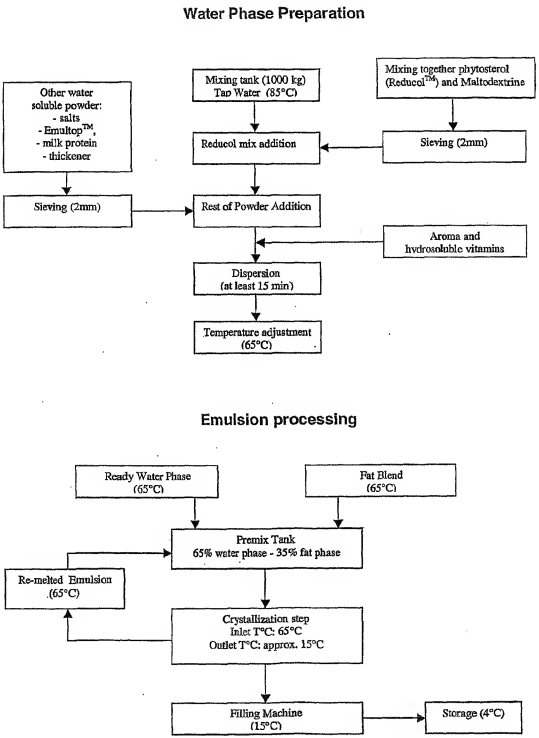
Fig 1:Low Fat Spread Preparation Flow Sheet



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/575 A23D7/015 A23D7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K A23D A23G A23C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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